Palladium-Catalyzed Tandem Bis-allylation of Isocyanates
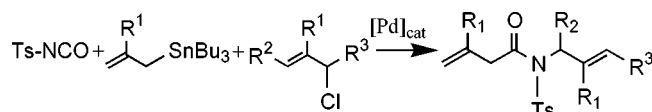
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ABSTRACT

A tandem bis-allylation of *p*-toluenesulfonyl isocyanate can be achieved by palladium-catalyzed three-component coupling reaction with allylstannanes and allyl chlorides. A high level of regioselectivity can be obtained by the appropriate choice of the allylic substituents. The reaction mechanism and the regiochemistry of the reaction can be explained by formation of an amphoteric bis-allylpalladium intermediate. This bis-allylpalladium intermediate undergoes an initial electrophilic attack on one of the allyl moieties followed by a nucleophilic attack on the other.

Isocyanates have proven to be useful and versatile reagents in allylpalladium chemistry.[1,2] These reagents have been used extensively in palladium-catalyzed ring-opening cyclization[1] of vinylaziridines and vinyl epoxides, as well as in telomerization of butadiene.[2] A common feature of these reactions is that an initial electrophilic attack of the carbonyl carbon of the isocyanate generates an anionic species, which performs a nucleophilic attack on the (η^3-allyl)palladium intermediate of the catalytic transformation. We have now found that toluenesulfonyl isocyanate (**1**) undergoes a similar type of reaction with allylstannanes and allyl chlorides in the presence of catalytic amounts of palladium (Scheme 1).

Scheme 1
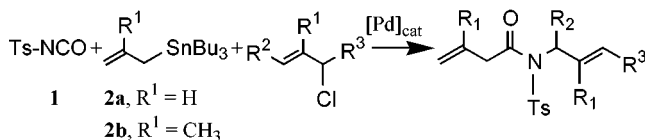
In this process both the carbon and the nitrogen atoms of isocyanate **1** can be alkylated regioselectively with different allyl moieties (Table 1) in good yield.

In a typical reaction the corresponding allyl chloride (0.38 mmol) and Pd(PPh$_3$)$_4$ (5 mol %) in THF (1 mL) were stirred for 15 min at room temperature under an Ar atmosphere. Thereafter, allylstannane (0.38 mmol) was added and this mixture was stirred for 5 min. After addition of Ts-NCO (0.32 mmol), the reaction mixture was stirred for the temperatures and times listed in Table 1. The reaction mixture was then diluted with ether and treated with a saturated KF solution. After filtration through Celite, the organic phase was washed with water and brine, dried over MgSO$_4$, and concentrated. The products **4−9** were isolated by silica gel chromatography using a pentane−ether eluent.

The reaction was relatively fast (entries 1−2) with unsubstituted allyls (**2a** and **3a**), while in the presence of alkyl substituents (**3b−e**) a higher reaction temperature (60 °C) and a longer reaction time (3−8 h) had to be employed (entries 3−7). A shorter reaction time or lower temperature using **3b−e** as the allyl chloride component provided a considerable amount of the mono-allylated product after workup. On the other hand, a reaction temperature over 60 °C led to allylic rearrangement of the product. Using other catalyst sources, such as PdCl$_2$(PhCN)$_2$, did not improve the

(1) (a) Butler, D. C. D.; Inman, G. A.; Alper, H. *J. Org. Chem.* **2000**, *65*, 5887. (b) Larksarp, C.; Alper, H. *J. Am. Chem. Soc.* **1997**, *119*, 3709. (c) Baeg, J. O.; Bensimon, C.; Alper, H. *J. Am. Chem. Soc.* **1995**, *117*, 4700. (d) Trost, B. M.; Van Venkren, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444. (e) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1988**, *110*, 7933. (f) Trost, B. M.; Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792. (g) Hayashi, T.; Yamamoto, A.; Ito, Y.; *Tetrahedron Lett.* **1988**, *29*, 99.

(2) Ohno, K.; Tsuji, J. *Chem. Commun.* **1971**, 247.

Table 1. Palladium-Catalyzed Three-Component Reaction of TsNCO, Allylstannanes **2a,b**, and Allyl Chlorides **3a–e**[a]

Entry	Allyl stannane	Allyl chloride	Reaction[b] conditions	Product	Yield[c]
1	**2a**	⟍⟋Cl **3a**	40/1	**4**	65
2	**2a**	**3a**	40/1	**4**	56[d]
3	**2a**	**3b**	60/3	**5**[e]	62
4	**2a**	**3c**	60/4	**6**	60
5	**2a**	**3d**	60/4	**7**	42
6	**2b**	**3e**	60/3	**8**	71
7	**2b**	**3b**	60/8	**9**[e]	52

[a] Unless otherwise stated the reactions were conducted in THF using 5 mol % of $Pd(PPh_3)_4$. [b] Temperature (°C)/reaction time (h). [c] Isolated yield. [d] 5 mol % of $PdCl_2(PhCN)_2$ and 10 mol % of PPh_3 were used as catalyst. [e] *cis/trans* ratio 1:5.

yield of the reaction (entry 2). Only the unchanged starting material could be recovered, when 1,3-dialkyl-substituted allylstannanes were employed in place of **2a,b**.

Phenyl and nitrophenyl isocyanates reacted more sluggishly than **1**, and the catalytic reaction was stopped after mono-allylation of the reagent (Scheme 2).

Scheme 2
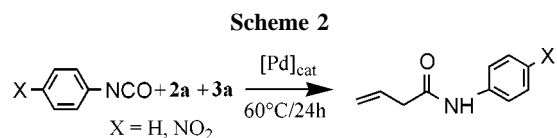
Analogous palladium-catalyzed three-component coupling reactions using allylstannane (**2a**) and allyl chloride (**3a**) have recently been applied to diallylation of benzylidenemalonitrile and its congeners by Yamamoto and co-workers.[3a] These authors[3b] found that benzyne derivatives also undergo three-component coupling with **2a,b** and **3a** or **3e**. Nicholas and co-workers[4] performed a similar coupling reaction using carbon dioxide in place of benzyne. Thus, the present reaction (Scheme 1) can be considered as a new extension of the palladium-catalyzed three-component coupling reaction using an isocyanate as the substrate (entries 1 and 6). An important feature of the tosyl isocyanate based coupling reactions is that a very high regioselectivity can be achieved when terminally alkylated allyl chlorides (R^2, $R^3 \neq$ H) are employed (entries 3–5 and 7). In previous publications[3,4] it was pointed out that using different substituent patterns on the allyl chloride and allystannane components leads to formation of regioisomer mixtures. For example, when **2a** and **3e** are reacted with benzyne or CO_2, an almost statistical mixture of diallylated products is formed, including all possible homo- and cross-coupling products.[3b,4] We have also found that in the three-component coupling reaction of **1**, **2a**, and **3e**, a mixture of two different regioisomers and homo-coupling products **4** and **8** was formed (Scheme 3). A

Scheme 3
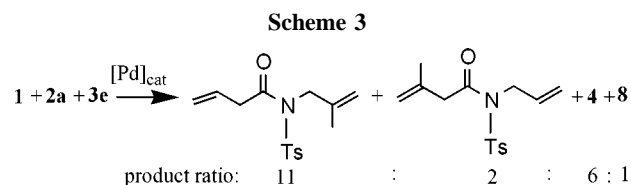
similar reaction mixture was obtained when a more bulky allylstannane, **2b**, and the unsubstituted allyl chloride **3a** are employed. Clearly, the presence of alkyl substituents at both the C1 and C3 positions in the allyl chloride component (**3b–d**) is a prerequisite of the high regioselectivity. Furthermore, by using **3b–d** in this process the formation of the homo-coupling products (e.g., **4** and **8**) can be completely avoided.

Mechanistic Considerations. Yamamoto and co-workers[5] have shown that reaction of **2a** with (η^3-allyl)palladium complexes, such as **10**, leads to formation of bis-allylpalladium species (**11**). In contrast to mono-allylpalladium complexes, bis-allylpalladium complexes are nucleophilic and react readily with electrophiles.[5–7] Furthermore, it has been demonstrated[5] that under catalytic conditions bis-allylpalladium complexes may undergo an initial *electrophilic* attack on one of the allyl moieties followed by a *nucleophilic* attack on the other. Accordingly, a plausible mechanism of the catalytic cycle is given in Scheme 4. The first step is an oxidative addition of the palladium(0) catalyst to allyl
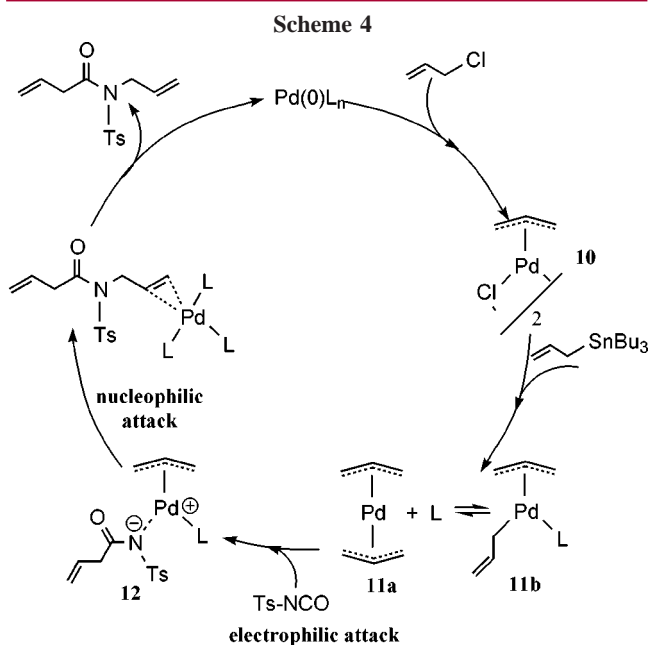
(3) (a) Nakamura, H.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 8113. (b) Yoshikawa, E.; Radhakrishnan, K. V.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 729.

(4) Franks, R. J.; Nicholas, K. M. *Organometallics* **2000**, *19*, 1458.

(5) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641.

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(7) (a) Szabó, K. J. *Chem. Eur. J.* **2000**, *6*, 4413. (b) Solin, N.; Narayan, S.; Szabó, K. J. *J. Org. Chem.* **2001**, *66*.

Scheme 4

10

11a   **11b**

nucleophilic attack

electrophilic attack

Ts-NCO

12

Scheme 5

13a, $\Delta E = 0$ more stable

13b, $\Delta E = 2.7$ kcal mol^{-1} less stable

(L = PH$_3$)

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chloride, which results in mono-allylpalladium complex **10**. This complex reacts with allylstannanes, giving a bisallylpalladium complex[5] (**11**).

In the presence of phosphine ligands (L = PPh$_3$) this complex coordinates one of the allyl groups in an η^1-fashion (**11b**).[7] Recent mechanistic studies showed[7] that the η^1-allyl moiety in bis-allylpalladium complexes is highly reactive toward electrophiles. Thus, the η^1-allyl moiety of **11b** undergoes electrophilic attack by the carbonyl carbon of **1**, affording a mono-allylpalladium complex and an allylated N-nucleophile (**12**). The second allylation reaction involves a nucleophilic attack by this N-nucleophile on the allyl moiety of the mono-allylpalladium intermediate. This nucleophilic attack regenerates the palladium(0) catalyst and provides the bis-allylated isocyanate derivative (e.g., **4**) product.

In the case of substituted allyls, the above reaction may result in two (entries 3 and 7) or four regioisomers (entries 4−5) depending on the location of the initial electrophilic attack and on the regioselectivity of the subsequent nucleophilic attack. The structure of the single regioisomers obtained clearly indicates that the electrophilic attack takes place on the unsubstituted allyl moiety of the bis-allylpalladium intermediate. This can be explained by the fact that the substituent effects of the alkyl groups depend on the coordination state (η^1- vs η^3-coordination) of the allyl moiety in the bis-allylpalladium intermediate. Theoretical calculations show[7] that the η^3-dimethyl-substituted complex (**13a**) is more stable than its η^1-dimethyl-substituted (**13b**) counterpart (Scheme 5). Furthermore, the activation barrier of the electrophilic attack is lower for **13a** than for **13b**.[7b] The formation of **6** and **7** alone indicates that even the nucleophilic attack of the monoallylpalladium complex (cf. **12**) is highly regioselective.

The mild conditions and short reaction time for the three-component coupling of **2a**, **3a**, and **1** (entry 1) indicate that
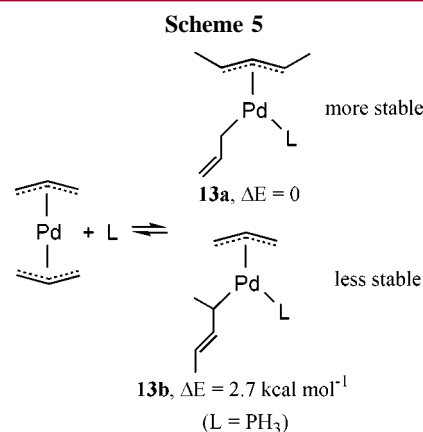
the electrophilic and nucleophilic attack on the unsubstituted allyls is probably very fast. However, when **3b−d** is employed, the nucleophilic attack on the η^3-allyl moiety bearing bulky alkyl substituents slows down the reaction (entries 3−5 and 7).

As mentioned above, the catalytic reaction does not proceed with 1,3-dialkyl-substituted allylstannane derivatives. This is probably due to the fact that the transmetalation of **10** with bulky allylstannanes is more difficult than the corresponding transmetalation with **2a,b** (cf. **10** → **11** in Scheme 4). The lower electrophilicity of phenyl isocyanate (Scheme 2) compared to **1** explains the observation that the reaction is more sluggish with Ph-NCO than with Ts-NCO.

The high reactivity of the η^1-coordinated allyl moiety toward isocyanates can also be demonstrated by quantum chemical molecular modeling. Density functional calculations[8] indicate that electrophilic attack on the η^1 moiety of the bis-allylpalladium intermediate (Scheme 6) proceeds with

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Scheme 6

H-NCO
$\Delta E_{act} = 11.7$ kcal mol^{-1}

11b

$\tau = 88.6°$
1.953 Å

14, TS

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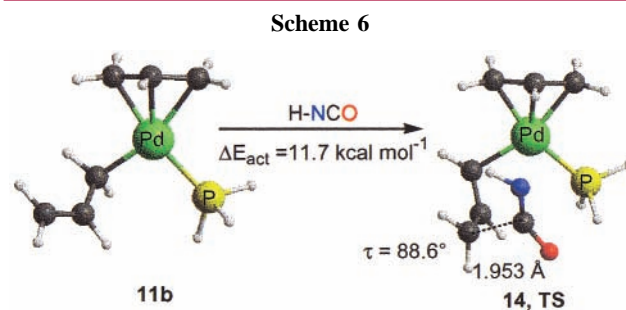
a remarkably low activation energy (11.7 kcal/mol). This activation barrier is in the range of the corresponding activation energies calculated for electrophilic attack by formaldehyde (7.2 kcal/mol) and acrylonitrile (14.2 kcal/mol).[7] It was shown that various derivatives of these species, such as benzaldehyde and benzylidenemalonitrile, react

(8) The geometries were fully optimized employing a Becke-type[9] three-parameter density functional model B3PW91 using a double ζ(DZ)+P basis constructed from the LANL2DZ basis augmented by one set of d-polarization functions on the heavy atoms. For further details see refs 7a,b.

readily with bis-allylpalladium intermediates occurring in palladium-catalyzed two- or three-component coupling reactions.[3a,5]

Transition state structure **14** reveals two important factors which facilitate the electrophilic attack on bis-allylpalladium complex **11b**: (i) the hyperconjugative interactions[10] in the η^1-moiety, as shown by the C1−C2−C3−Pd torsional angle τ (88.6°),[7] and (ii) the electrostatic interactions between the palladium atom and the nitrogen atom of HNCO. Electron-withdrawing substituents, such as a tosyl group, on the nitrogen increase the electrophilicity of the carbonyl carbon of the isocyanate, which is expected to lower the activation barrier of the electrophilic attack.

In summary, we have shown that **1** can be allylated on both the carbon and nitrogen atoms of the isocyanate functionality in palladium-catalyzed three-component coupling with allylstannanes and allyl chlorides.[11] A remarkably high regioselectivity can be achieved using **3b−e** as allyl chloride component. The reactivity of **1** and the regioselectivity of the allylation reaction can be rationalized on the basis of the formation of a bis-allylpalladium intermediate in the catalytic transformation.

(9) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
(10) These hyperconjugative interactions occur between the π^* and the d_σ(Pd−C) MOs in the η^1-allyl moiety. This hyperconjugation is most intensive when $\tau = 90°$, since this torsional angle ensures an optimal orbital overlap between π^* and d_σ(Pd−C).[7]

(11) After preparation of this Letter, we found a very recent, independent study by Yamamoto and co-workers including the coupling reaction of **2a**, **3a**, and Ts-NCO (Table 1, entry 1). Nakamura, H.; Aoyagi, K.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 372.